REMARKS

The amendment to claim 25 is supported throughout the specification and examples. See, particularly, pages 7, 11 and 36. Claim 28 is supported by the specification at pages 7-11. Claims 29-40 are supported as set forth above for claim 28. More particularly, claim 29 corresponds to original claim 15; claim 30 corresponds to original claim 16; claim 31 corresponds to original claim 17; claim 32 corresponds to original Claim 18; claim 33 corresponds to original claim 19; claim 34 corresponds to original claim 20; claim 35 corresponds to original claim 21; claim 36 corresponds to original claim 22; claim 37 corresponds to original claim 23; and claim 38 corresponds to original claim 24. Claim 39 is supported by the specification at page 14; claim 40 is supported by the specification at page 9. As such, the amendments do not constitute new matter, and their entry is respectfully requested.

Applicants are submitting corrected drawings along with this Amendment.

Claims 15-23 and 25-27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 94/18992 (McCormick) in view of Raj et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The prior art does not teach or suggest a method of using an E2F responsive promoter as claimed to obtain the selective expression demonstrated. The prior art combination acknowledges that E2F responsive promoters respond to E2F in a *cell cycle dependent* manner (see Raj at 1286). Thus, the prior art would not have expected the selective expression systems taught herein.

As taught in the specification and explicitly exemplified, the present system is not based on the greater proliferation of malignant cells. Applicants explicitly taught that the system was

not the same as one that was proliferation based. This can clearly be seen when one looks at the examples. See, for example, the discussion at pages 31-36 and the accompanying Figures. The tumor specificity of the present invention was first shown in the experiment at pages 31-32 and Figure 3. A vector containing an E2F responsive promoter and βgal was injected into rats having normal brains or brains with an established glioma. The normal rat brains injected this way showed virtually no β galactosidase staining, whereas injection into rats with established gliomas resulted in extensive staining of the tumor itself (see, Figures 3C and 3D). A control in which the βgal gene was under the control of a very strong constitutive promoter (CMV) resulted in extensive staining in both the normal brain and the glioma.

As explained at pages 31-33 of the specification, different possibilities could account for this activity. One could be that the malignant cells are cycling to a greater extent than the normal cells. As indicated therein, a second possible explanation was that the glioma cells resulted in an expression level that not even mitotically active normal cells could achieve. In a first set of experiments that is described in the paragraph bridging pages 32 and 33 and described in Figure 4, normal rats underwent a partial hepatectomy followed by injection of either βgal under the control of a constitutive promoter or βgal under the control of an E2F responsive promoter. Four days later, livers were harvested and stained for βgal activity, proliferating nuclear antigen and the adenovirus fiber protein. The results showed the presence of a large number of normal proliferating cells which did not express the reporter gene (Figure 4C,D). The data taught that the high level of the E2F promoter-mediated transgene expression in vivo was **not** a function of active cell cycling (i.e. proliferation).

In a second set of experiments described at pages 34-36, the herpes thymidine kinase(tk) gene was put into a vector under the control of either an E2F responsive promoter or a strong

constitutive promoter. The results again confirmed the difference in selectivity between the normal cells and malignant cells.

These results and the background supporting them are further explained by Dr. Kaelin in his Declaration submitted with the prior response. As explained therein, a gene linked to an E2F responsive promoter can be in one of three states – 1) fully repressed by a specific complex (pRB/E2F); 2) in a basal state where there is no repression; or 3) fully activated as a result of having large amounts of E2F that is not complexed with pRB, i.e., "free" E2F. The consequence for gene expression of these three different situations is in no way taught or suggested by the prior art. For example, Raj was looking primarily at a protein that was specifically taught as being something other than an E2F species, i.e. "novel glial E2F1-associated proteins, or GEAPs that bind to E2F1 site as a complex with a distinct mobility, specificity and affinity." See the paragraph bridging pages 1280 and 1281.

Thus, Raj provides absolutely no basis for looking at levels of E2F and determining whether they would result in greater expression of a gene operably linked to an E2F responsive promoter than a non-malignant cell, as required by step a) of claim 25, or to look at whether a malignant cell expresses sufficient E2F to activate an E2F responsive promoter to result in expression of higher levels of a gene operably linked to the E2F responsive promoter. McCormick adds nothing to this with respect to selectivity.

In contrast, as discussed above, Applicants taught in this specification and particularly in the Examples that the selectivity achieved and claimed herein is not a result of greater proliferation of malignant cells, but reflects a fundamental difference between a malignant cell and a non-malignant cell. This selectivity is in no way taught.

In the previous response, the Examiner indicated that the discussion by Dr. Kaelin did not relate to the claim recitations. Applicants respectfully disagree but they have made explicit that which was implicit – namely, that the selective expression of the gene in a malignant cell claimed by claim 25 is a result of the malignant cell expressing sufficient E2F to cause increased expression of that gene when compared to mitotically active (proliferating) non-malignant cell. Claim 28 is similar in pointing out the selectivity is based on the difference between malignant and non-malignant cells.

Accordingly, Applicants respectfully submit that this rejection of the claims should be withdrawn.

Claims 15-27 were rejected pursuant to 35 U.S.C. §103(a) as being unpatentable over WO 94/18992 (McCormick) in view of Raj et al. as applied above and further in view of US patent 6,310,045 (the '045 patent). Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The addition of the '045 patent does not overcome the deficiency of the combination of McCormick in view of Raj, described above. Applicants notes that the Examiner discussed Raj at page 8 of the Response and indicated that Raj at page 1285, column 2, discusses the importance of E2F in human glioma cells for activation of the endogenous E2F responsive promoter. Applicants respectfully submit that a fair reading of Raj shows that E2F was relatively unimportant, and worked in a cell cycle dependent manner (see page 1286). Additionally, Raj taught that expression of anti-sense E2F1 showed no significant effect on transcriptional activities of the test promoters. And, specifically Raj concludes that there is a functionally distinct complex i.e., GEAP that is negatively influenced by E2F1. The discussion with respect to Raj, when read in its

entirety, is that E2F and E2F responsive promoters interact in a cell-cycle dependent manner and would thus indicate that there should be no difference between its effect in normal proliferating cells and malignant cells. The addition of the '045 patent adds nothing to this deficiency.

Accordingly, Applicants respectfully submit that this rejection of the claims should be withdrawn.

In view of the foregoing, Applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

If any additional fee is required, please charge Deposit Account No. 50-0850.

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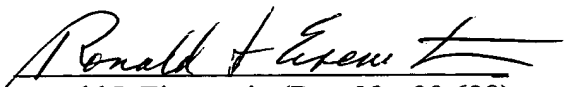
Respectfully submitted,



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